alternative spacer, appropriate in vitro or in vitro and clinical data must be presented.[3]

The proposed "amount of drug within the respirable range" is not enough to ensure equivalence from an in vitro point of view since the whole aerodynamic particle size distribution has to be compared.[3] If comparative in vitro determination using a validated method does not show equivalence, a clinical comparison is required. This clinical comparison must include an assessment of systemic safety through investigation of equivalence based on pharmacokinetic data or pharmacodynamic data.[3]

From an efficacy viewpoint the study must be sensitive enough to discriminate between spacers. For a study to have assay sensitivity at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other. Consequently, the proposed study design to assess "improvement of spirometric parameters" does not comply with the regulatory requirements[3-5] and the state of the art,[2] consisting of the estimation of the relative potency. Furthermore, the authors have neither compared the results statistically nor predefined the acceptance range to conclude that both VHCs are equivalent. Therefore, it is not possible to conclude that "both of the VHCs tested were suitable for use in the delivery of salbutamol."[1] The new VHC should be compared properly to be used and it should be used only with those pMDIs investigated.

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Response

To the Editor:

In reply to the response by García-Arietato regarding our previous correspondence,[1] we are pleased to see that we have attained our initial objective of drawing attention to and provoking discussion on the unacceptable situation concerning drug delivery through pressurized metered-dose inhalers (pMDI) and spacers. The main problem is that summaries of product characteristics of drugs in pMDIs currently available on the market often do not contemplate the use of valved holding chambers (VHCs), even if evidence suggests that they should not be used without them in order to avoid oropharyngeal deposition, and do not report instructions for use or therapeutic dose when administered with specific VHCs. Moreover, it has even been suggested that plastic or glass bottles can be used instead of VHCs. On the basis of this evidence, many patients probably do not use drugs properly delivered by pMDIs and do not receive the optimal therapeutic dose.

We agree that if a pMDI has been designed for use with a specific spacer it should always be used with this named spacing device.[2] In this case, however, both should be present in the same package to avoid misuse and must be reported in the product warnings, for example, "These instructions are not necessarily valid when this pMDI is used with other spacers."

Aerosol therapy is a complex process that depends on nebulizer performance and patient features. In order to avoid errors, these variables should be studied separately. The amount of drug within the respirable range is an objective parameter to quantify the amount of drug available at the end of the spacer system and potentially capable of reaching the lower airways. This simple method has been suggested to standardize first-step aerosol therapy delivery[3] and is currently the only way of assessing the effective amount of drug administered. Moreover, if comparative in vitro determination does not show equivalence, it is highly likely that either will clinical comparison. If pMDI drugs are to be used with different spacers, instructions must be given about how to make the same effective amount of drug to be administered available at the end of each spacer. Our results were supported by statistical analysis, particularly a general linear model for repeated measures using type of treatment and sex as factors and age as covariate. FEV_1 ($F = 28.733$; $P < .001$) and peak expiratory flow ($F = 25.879$; $P < .001$) were shown to increase significantly after both treatments.

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Occlusion and Malposition of Small-Bore Chest Tubes for Pleural Infection

To the Editor:

We read with great interest the recent study by Rahman et al (March 2010),[1] which suggests that smaller tubes are as effective for the treatment of pleural infection as larger-bore tubes, while causing less pain. However, no mention was made of two complications that smaller tubes may be more prone to: malposition and occlusion.

Although we are not aware of published data, common sense suggests that occlusion of chest tubes used to drain thick fluid, such as pus, may occur more readily with small-bore tubes. Remérand et al[2] showed that chest tube malposition is fairly common (30% in their series), and that avoiding the use of a trocar reduces the risk of malposition. There are, however, no data regarding guidewire insertion.

Despite the fact that tube size was not randomly assigned, we would be very interested to know what the incidence of these complications was in the authors' series. If they were more frequent with small-bore tubes, that would be an argument against the use of these tubes. Obviously, both this hypothesis and the authors' conclusion that small-bore tubes yield similar clinical outcomes to large-bore tubes will have to be tested in randomized studies.

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Response

To the Editor:

We share the interest and concern of Drs Atchabahian, Laplace, and Tazarourte in the quality of care patients receive with chest tube drainage. We agree that there is a compelling need for randomized trials to accurately define efficacy and safety of different tube sizes and insertion techniques. Until such trials are completed, it is not possible to know with certainty which tube types are in the best interests of patients, and we must rely on nonrandomized data sets. Against this background, our cohort represents the largest comparative study to date and so helps to inform the debate about this important treatment.

Although it seems intuitive that smaller tubes become blocked during the drainage of infected purulent fluid, there is extensive observational (nonrandomized) literature suggesting that this is not the case in practice, particularly with regular flushing.[1,2] The lack of therapeutic advantage in our large series[3] supports the conclusion that there is no clear disadvantage to smaller bore tubes. Within our study, the rate of malposition or occlusion requiring reinsertion of a second tube is captured within the results and discussed in the article. We continue to believe that our data provide preliminary encouraging evidence that smaller bore tubes may achieve as good a clinical outcome with less pain for patients, and we eagerly anticipate the results of well-designed randomized trials to definitively assess whether this is true.

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